Message

From: tbstarr@mindspring.com [tbstarr@mindspring.com]
Sent: 6/4/2013 4:07:51 PM
To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]
Subject: Re: presentation of rat tumor data example at ARA
Attachments: ARA.Starr.final.ppt

Ravi:

At the ARA workshop, I presented MY multistage model analysis of the rat tumor data vs. airborne formaldehyde concentration, and I described it as a "typical top down analysis". I did not attribute this analysis data to you or to EPA (see the attached Powerpoint file for my ARA workshop presentation slides, particularly #15-22). Furthermore, I did not refer to your counter-example analysis of the rat tumor data at all.

When we first proposed the bottom up approach back in 2010, there were no top down analyses based on adducts, and no attention was being paid to endogenous exposure levels in the formaldehyde risk assessment, or any other risk assessment. The bottom up approach I presented at the ARA workshop is relatively unchanged from what I presented to you and other EPA staff at our earlier 27 February 2013 meeting.

The main differences between the ARA presentation and my previous 27 February 2013 presentation are:

1) use of the multistage model (Global86 version) instead of a Weibull model (BMDS version) to fit the rat tumor data vs. ppm and obtain both MLE and upper 95% confidence bound estimates for the top down additional risk at 1 ppm (see slide 18). I was motivated to make this change by Paul White's comments at the 27 February meeting about the BMDS Weibull model upper bound risk estimates being nonlinear;

2) use of the Lu et al. (2011) endogenous adduct concentration estimate after a single 2 ppm exposure of rats for 6 hours (6.09 +- 1.52 (se)) to produce a lower 95% confidence bound estimate of the endogenous adduct concentration (COL). I used this value to make my rat bottom up analysis more directly comparable to what we had already done for the human bottom up cancer analyses based upon measured adduct concentrations in monkeys following two 6 hour exposures to 2 ppm. This change was also motivated by my being unable to reproduce the mean endogenous adduct value of 4.7 +- 1.8 (sd) value that is cited in Lu et al., (2011). I still looking for the source of this number;

3) use of an upper 95% confidence bound estimate of the background rat tumor risk (POU = 13.16e-4) instead of the central estimate of 1/3602) in the bottom up slope factor calculation . Accommodating the substantial uncertainty inherent in P0 due to small numbers is very important in the rat analysis, whereas in the human analysis, the uncertainty in P0 is small enough to be safely ignored. Compare slides 12 and 19 and also see our discussion of this point in the bottom up paper (Starr and Swenberg (2013)).

4) adjustment of the corresponding exogenous adduct concentration (Cx6 = 0.19 +- 0.04) to the equivalent steady state value (Cxss = 0.531) using the one-compartment PK model with a 63 hour half-life (multiplying by 15.65), coupled with additional multiplicative scaling by factors of 6/24 and 5/7, since exposure during the cancer bioassays was only for 6 hr/day, 5 day/wk. This stretches out the exogenous adduct exposure scale relative to endogenous adducts, which are always at steady-state, so it could make a substantial difference in your counter-example analysis, which made no adjustments to the 6 hour exogenous adduct measurements.

I hope this clarifies what I presented at the ARA workshop, and I look forward to continued open dialogue on this important topic. Let me know if you have any questions.

Best regards,
Tom Starr

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On 6/1/2013 11:22 AM, Subramaniam, Ravi wrote:
> Dear Tom:
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> This is with reference to your presentation at the ARA workshop.
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> In the workshop, an analysis of the rat tumor data was presented and attributed to EPA. I assume your reference was to the counter-example I provided you in our email exchange to illustrate that the bottom up approach underestimates the slope of a fit to the rat tumor data. However, what I sent you was very different even at a conceptual level from what was presented at the workshop.
> As I understand it, the bottom up approach is based on adduct levels as the dose metric, so the counter-example I had shared with you was similarly based on adduct levels as the dose-metric, not exposure concentration in ppm.
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> I realize that communications between us are not confidential, but I also note that when sharing the counter example with you I had not understood that you were going to present it, even if done so accurately, in a conference. That does raise the hurdle to freely sharing ideas in dialogue. I had used mean adduct levels for the dose-metric since the purpose was illustrative; for any formal presentation, I would have used or made reference to conceptually similar results with lower bounds.
>
> If I am correct that your reference was to what I had shared with you, I hope you will correct them before further distribution by the ARA. If you continue to make reference to EPA materials, at a minimum I ask that you accurately characterize what was sent to you. I will be glad to discuss further if any of this is not clear.
>
> Best Regards,
> Ravi.
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